View metadata, citation and similar papers at core.ac.uk

brought to you by CORE

provided by Scholarly Commons

University of the Pacific
Scholarly Commons

College of the Pacific Faculty Articles

All Faculty Scholarship

1-1-2015

Acylation of trans-2-substituted cyclohexanols: The impact of substituent variation on the pyridine-induced reversal of diastereoselectivity

Sven Hackbusch
University of the Pacific

Andreas H. Franz
University of the Pacific, afranz@pacific.edu

Follow this and additional works at: https://scholarlycommons.pacific.edu/cop-facarticles

Part of the Chemistry Commons

Recommended Citation

Hackbusch, S., & Franz, A. H. (2015). Acylation of trans-2-substituted cyclohexanols: The impact of substituent variation on the pyridine-induced reversal of diastereoselectivity. *ARKIVOC, 2015*(7), 172–194. DOI: 10.3998/ark.5550190.p009.321
https://scholarlycommons.pacific.edu/cop-facarticles/160

This Article is brought to you for free and open access by the All Faculty Scholarship at Scholarly Commons. It has been accepted for inclusion in College of the Pacific Faculty Articles by an authorized administrator of Scholarly Commons. For more information, please contact mgibney@pacific.edu.

Acylation of *trans*-2-substituted cyclohexanols: the impact of substituent variation on the pyridine-induced reversal of diastereoselectivity

Sven Hackbusch and Andreas H. Franz*

Department of Chemistry, University of the Pacific, 3601 Pacific Avenue, Stockton, CA 95211, USA.
E-mail: afranz@pacific.edu

DOI: http://dx.doi.org/10.3998/ark.5550190.p009.321

Abstract
Numerous methods for the stereoselective synthesis of chiral compounds exist in the literature, which use chiral templates or catalysts. Only in a limited number of cases have achiral catalysts been shown to significantly influence the stereochemical outcomes of reactions. Previous studies in our laboratories have revealed the achiral acyl-transfer catalyst pyridine to alter the stereochemical outcome of the reaction of racemic *trans*-2-substituted cyclohexanols with racemic 2-chloropropionyl chloride and cause a reversal of diastereoselectivity. The current paper presents the application of the reaction scheme to a wider number of substrates and reveals the importance of the heteroatom in the *trans*-2-substituent.

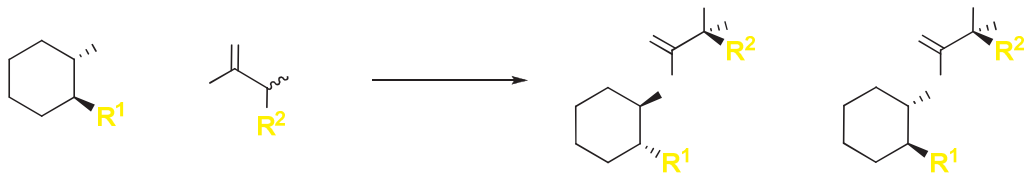
Keywords: Reversal of diastereoselectivity, acylation, achiral catalyst, neighboring group influence

Introduction

The precise control of stereochemistry in organic synthesis is highly desirable and the use of a single catalyst for obtaining exclusively one of multiple products of a stereoselective reaction describes an ideal scenario, which has been realized in some cases.[1-3] Chiral substrates influence the stereochemical outcomes of their own transformations.[4] In addition, stereoselectivity can be impacted by a number of factors, such as solvent polarity or temperature. Examples for the complete reversal of stereoselectivity based on these factors exist in the literature.[5-7] In organometallic catalysis, chiral ligands can be utilized to control enantio- or diastereoselectivity. In some cases, even achiral additives have been shown to influence the stereochemical course of reactions,[8-10] and π-π stacking can play an important role as well.[11,12] Our lab has previously shown that pyridine and derivatives thereof are able to catalyze the acylation of several racemic

 ©ARKAT-USA, Inc.

trans-2-substituted cyclohexanols, carrying e.g. tolylsulfanyl- or tolyloxy-substituents, with (±)-2-chloro-propionyl chloride while at the same time reversing the diastereoselectivity of the reaction.[13] A linear correlation between the amount of pyridine used and the diastereoselective outcome of the reaction was observed.[14] The purpose of this study was to further investigate this relationship and to probe the substrate scope for the reversal of diastereoselectivity with pyridine. Here, we provide a rationale for the previously observed catalyst-loading effect and show that pyridine is able to reverse the diastereoselectivity for the reaction of a variety of *trans*-2-substituted cyclohexanols with (±)-2-chloropropionyl chloride ((±)-**14**) and (±)-2-chloro-2-phenylacetyl chloride ((±)-**15**) in the presence of an auxiliary base, as depicted in Scheme 1.



Scheme 1. Reaction scheme for the acylation of racemic *trans*-2-substituted cyclohexanols with racemic acyl chlorides in the (i) absence or (ii) presence of pyridine (0.1 eq) and ProtonSponge® (1.0 eq) as auxiliary base. R_1 = variable (see Scheme 2), R_2 = Me ((±)-**14**), R_2 = Ph ((±)-**15**.

Results and Discussion

In our initial studies we focused in greater detail on the concentration-dependence of the observed diastereomeric ratio (*dr*) on pyridine. While equimolar amounts of pyridine or dimethylaminopyridine (DMAP) led to the reversal of *dr* compared to the uncatalyzed reaction (Table 1, Entries 1+3), use of catalytic amounts gave *dr*'s closer to the uncatalyzed reaction (Table 1, Entry 2). Additionally, our studies had previously revealed that non-nucleophilic bulky bases such as trimethylamine gave approximately 1:1 ratio of diastereomers for the product (Table 1, Entry 4). However, when using DMAP in catalytic quantities (0.1 equivalents) with one equivalent of trimethylamine, the overall yield was improved and the observed *dr* was comparable to the case of equimolar amounts of DMAP (Table 1, Entry 5). This effect of an auxiliary base was also seen when using a basic ion exchange resin (Amberlite IRA-400 OH; Table 1, Entry 6).

 ©ARKAT-USA, Inc.

Table 1. Removal of catalyst-load dependence through the addition of auxiliary base, using 0.1 mmol amounts of (±)-**1** and (±)-**14** in 1 mL CH_2Cl_2 in the presence of 0.1 mmol pyridine for 24 h at rt

Entry	Catalyst - mol%		Isolated Yield	*dr* (A:B)
1	-/-		40%	1**:2.0**
2	DMAP	10	35%	1**:1.7**
3	DMAP	100	47%	**2.6:**1
4	Et_3N	103	46%	1**:1.1**
5	DMAP + Et_3N	10+100	76%	**2.8:**1
6	pyridine + Amberlite	10+ 100	35%	**3.0:**1

The reason for this improvement in diastereoselectivity and yield through the addition of an auxiliary base is possibly the more effective neutralization of the hydrochloric acid which is released as a side-product of the reaction. When pyridine (or DMAP) is used in catalytic amounts, it is protonated by HCl over the course of the reaction and thus becomes unavailable for catalysis. This reverts the reaction back to the non-catalyzed reaction pathway which yields opposite diastereoselectivity. The effect is an overall reduction of the *dr*. The addition of an auxiliary base causes its protonation in the place of pyridine, leaving the latter to remain available to catalyze the acylation reaction. The effect is an overall improvement of the *dr*.

Next, the reaction conditions were optimized to give highest yield. It was noted from previous experiments that despite full consumption of (±)-2-chloropropionyl chloride only relatively low yields of the desired ester were obtained. Thus, screening of the alcohol to acyl chloride ratio revealed the 2:1 ratio thereof to give optimal ester formation for use in further reactions (Table 2).

As shown in Table 3, a small number of potential auxiliary bases were screened to find optimal conditions for the reaction of racemic *trans*-2-substituted cyclohexanols with racemic acyl chlorides. Based on the best combination of yield and *dr*, ProtonSponge® (1,8-bis(dimethylamino)-naphthalene was chosen as a homogeneous auxiliary base to be employed in the reaction.

 ©ARKAT-USA, Inc.

Table 2. Screening of alcohol (±)-**1** to acyl chloride (±)-**14** ratio for optimal yield at a 0.1 mmol scale in 1 mL CH_2Cl_2 in the presence of 0.1 mmol pyridine for 24 h at rt. ([a] Determined by ^1H NMR.)

Entry	ROH (eq.)	AcylCl (eq.)	Consumption [a] (Acyl Cl)	Ester Yield[a]
1	1.0	2.0	100%	41%
2	1.0	1.0	100%	63%
3	1.5	1.0	100%	67%
4	2.0	1.0	100%	91%
5	3.9	1.0	100%	91%

With these improved catalytic reaction conditions in hand, we set out to investigate the source of the reversal of diastereoselectivity in the reaction. For this purpose, a small library of racemic *trans*-2-substituted cyclohexanols, carrying a variety of OR, SR and CH_2R motifs (where R=aryl, alkyl), was generated for substrate screening. The alcohols were allowed to react with two commercially available racemic acyl chlorides, (±)-2-chloropropionyl chloride (±)-**14** and (±)-2-chloro-2-phenylacetyl chloride (±)-**15**.

Table 3. Screening of auxiliary base using (±)-**1** (0.2 mmol) and (±)-**14** (0.1 mmol) in 1 mL CH_2Cl_2 for 24 h at rt. ([a] 1:1 ratio of reactants)

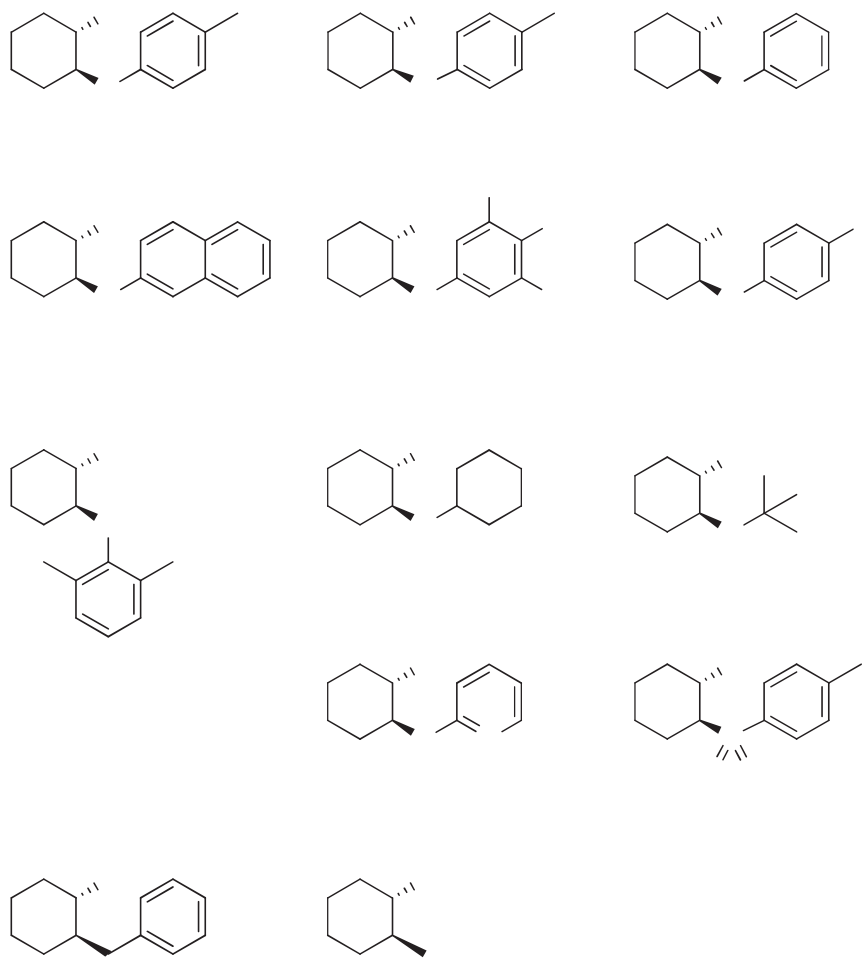
Entry	Catalyst (10 mol%)	Auxiliary base (1.0 eq)	Yield	*dr* (A:B)
1	-/-	-/-	24%	1**:2.7**
2	pyridine	Amberlite IRA-400 OH	60%	**3.7:**1
3	pyridine	ProtonSponge®	82%	**4.2:**1
4	pyridine	Amberlyst A21	40%	**5.4:**1
5[a]	DMAP	Et_3N	76%	**2.8:**1
6	pyridine	NaHCO3	31%	**3.6:**1

Compounds (±)-**1**-**7** and (±)-**10** were synthesized via basic epoxide opening of cyclohexene oxide in ethanol, while the carba-analog of (±)-**3** ((±)-**12**) was obtained from benzyl magnesium bromide and cyclohexene oxide in THF. The epoxide opening with electron-deficient nitrophenol was unsuccessful even under basic conditions. Compound (±)-**8** with a cyclohexyloxy substituent was obtained from the reaction of cyclohexene oxide and

 ©ARKAT-USA, Inc.

cyclohexanol under basic conditions. The OtBu-substitutent ((±)-**9**) was installed with catalytic amounts of $Cu(BF_4)_2$ as activator for the epoxide opening of cyclohexane oxide with *tert*-butanol. Compound (±)-**11** was synthesized from **1** through hydrogen peroxide oxidation in acetic acid. A second carba-analog ((±)-**13**) was commercially available.

The collection of racemic *trans*-2-substituted cyclohexanols was then reacted with (±)-2-chloropropionyl chloride in dichloromethane for 24 h at room temperature either (i) without or (ii) with the addition of pyridine and ProtonSponge® based on the established optimal reaction conditions elaborated above. Yield and *dr* were determined from the crude reaction mixture by ^{1}H NMR analysis and the diastereomers were assigned arbitrarily as A and B, with A being the diastereomer giving the more deshielded signal of the proton signal used for the determination of the ratio of diastereomers (compare Experimental section). The results of the substrate screening are summarized in Table 4.



Scheme 2. Generated library of racemic *trans*-2-substituted cyclohexanols.

 ©ARKAT-USA, Inc.

Little change in the *dr* in either (i) the absence or (ii) presence of pyridine and ProtonSponge® was observed when the aromatic moiety on the *trans*-2-substituent carried meta- or para-substituents (Table 4, Entries 1-6). The larger naphthyloxy-substituent in (±)-**4** also did not lead to higher *dr* in (ii), which indicated that extended π-π-stacking or other electronic effects on the aromatic moiety aside from the phenyl ring were not significant.

However, (±)-**7** and (±)-**11** showed a strong increase in *dr* in the catalyzed reaction. This may be a result of an increased bulk in the substrate close to the reaction center or a significant change in conformation of the substituent relative to the cyclohexanol moiety.

Table 4. Substrate screening of racemic *trans*-2-substituted cyclohexanols with (±)-**14** in the (i) absence or (ii) presence of pyridine (0.01 mmol) and ProtonSponge® (0.1 mmol) in 1 mL CH_2Cl_2 for 24 h at rt

Entry	ROH	rxn cond.	NMR yield	*dr* (A:B)	Entry	ROH	rxn cond.	NMR yield	*dr* (A:B)
1	(±)-**1**	I	40%	1**:3.2**	**15**	(±)-**8**	i	65%	1**:5.2**
2		Ii	80%	**3.2:**1	**16**		ii	50%	**3.3:**1
3	(±)-**2**	I	24%	1**:2.7**	**17**	(±)-**9**	i	94%	1**:5.5**
4		Ii	82%	**4.2:**1	**18**		ii	77%	**1.8:**1
5	(±)-**3**	I	22%	1**:2.7**	**19**	(±)-**10**	i	87%	**1.2:**1
6		Ii	73%	**3.7:**1	**20**		ii	81%	**1.9:**1
7	(±)-**4**	I	22%	1**:2.2**	**21**	(±)-**11**	i	0%	n.d.
8		Ii	70%	**3.8:**1	**22**		ii	34%	**15:**1
9	(±)-**5**	i	16%	1**:1.7**	**23**	(±)-**12**	i	53%	**2.0:**1
10		ii	57%	**3.8:**1	**24**		ii	77%	**1.2:**1
11	(±)-**6**	i	31%	1**:2.5**	**25**	(±)-**13**	i	90%	1**:2.2**
12		ii	61%	**3.7:**1	**26**		ii	64%	1**:1.6**
13	(±)-**7**	i	27%	1**:3.3**					
14		ii	63%	**7.5:**1					

Surprisingly, it was observed that alkyloxy-substituted compounds (±)-**8** and (±)-**9** gave higher absolute *dr* in the uncatalyzed reaction, contrary to the trend observed in aryloxy-substituted compounds. Although arguments related to electronics or sterics of these substituents and potential interactions with (±)-**14** could be made, the exact reason for this observation remains unknown and further exploration is needed to elucidate the cause.

 ©ARKAT-USA, Inc.

Compound (±)-**10** showed no reversal of *dr* between (i) and (ii). This is most likely the result of the pyridine moiety on the *trans*-2-substituent acting as an intramolecular acyl-transfer catalyst in the absence of pyridine. The carba-analogs (±)-**12** and (±)-**13** both did not show a reversal of diastereoselectivity upon the addition of pyridine and auxiliary base. This appears to be direct consequence of the lack of a heteroatom on the *trans*-2-substituent. The heteroatom may significantly influence the transition state energies in the reaction with the acyl transfer catalyst relative to the reaction without it or even actively participate in the mechanism, as previously proposed.[13] A heteroatom (oxygen or sulfur, in the cases above) may thus be essential for the reversal of *dr*.

Table 5. Substrate screening of selected racemic *trans*-2-substituted cyclohexanols with (±)-**15** in the (i) presence or (ii) absence of pyridine (0.01 mmol) and ProtonSponge® (0.1 mmol) in 1 mL CH_2Cl_2 for 24 h at rt

Entry	ROH	rxn cond.	NMR yield	*dr* (A:B)
1	(±)-**1**	i	32%	1**:1.1**
2		ii	85%	**2.5:**1
3	(±)-**2**	i	13%	1**:1.4**
4		ii	97%	**2.0:**1
5	(±)-**7**	i	18%	1**:2.0**
6		ii	>99%	**2.8:**1
7	(±)-**8**	i	69%	1**:6.8**
8		ii	> 99%	1**:10**
9	(±)-**11**	i	4%	1**:5.8**
10		ii	88%	**2.7:**1
11	(±)-**13**	i	99%	**1.7:**1
12		ii	> 99%	**1.1:**1

A small selection of racemic *trans*-2-substituted cyclohexanols was also subjected to (±)-2-chloro-2-phenylacetyl chloride (±)-**15** in the same reaction scheme as above. The results are shown in Table 5. The initial expectation that a bulkier acyl chloride would yield higher *dr* was not borne out by the data. Although reversal of diastereoselectivity was seen generally, the *dr* was lower in the majority of cases with (±)-**15** than with (±)-**14**. The reason for this may be that the replacement of a methyl group with a phenyl group in the γ-position on the acyl chloride leads to steric crowding in the transition state, meaning that stereodifferentiation is more

 ©ARKAT-USA, Inc.

successful with less sterically demanding acyl substrate. Curiously, no reversal of diastereoselectivity was observed for (±)-**8** (Table 5, Entries 7 and 8). The reason for this lack of reversal is not immediately apparent and warrants further study.

In order to further investigate the reason for the reversal of *dr* with the addition of pyridine, the transition state structures of the ester formation were computed at the B3LYP/6-31G* level of theory for (±)-**1**, (±)-**2** and (±)-**13** with (±)-**14** and the acyl-pyridinium intermediate of (±)-**14**, respectively, under basic conditions (alcoholate). However, the reversal of diastereoselectivities due to the introduction of pyridine was not borne out quantitatively by the computed relative transition state energies for the different diastereomeric transition states. (For full details, transition state energies and structures, see Supplemental Material.) Modeling of the reaction at a higher level of theory and potentially with consideration of the solvent may give a more accurate representation of the experimentally observed situation, especially given the fact that the observed *dr*'s would correspond to relatively small differences in the transition state energies. Instead, a qualitative interpretation of the computational results revealed some interesting observations that could help explain the experimentally observed reversal of *dr*.

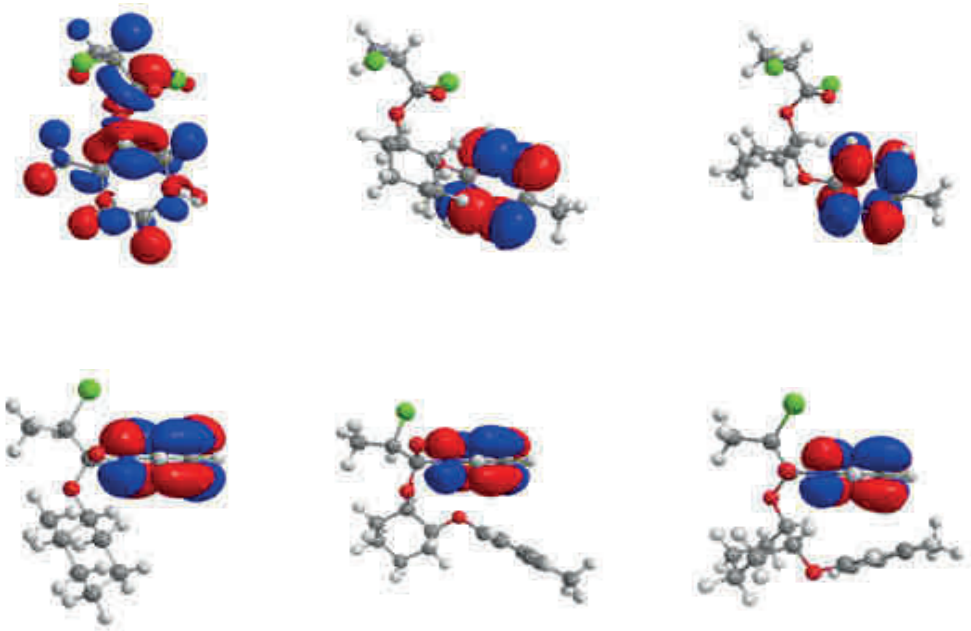


Figure 1. Representative transition state structures for the ester formation of (±)-**13** (top left structure) or (±)-**2** (top right two structures) with (±)-**14** or the acyl-pyridinium intermediate of (±)-**14** (bottom left for (±)-**2**, middle and right for (±)-**2**) under basic conditions (alcoholate) with the LUMO shown.

Figure 1 depicts a characteristic selection of the structures of the lowest transition states found for the respective reactions of (±)-**2** and (±)-**13** with their LUMO shown. The structures and geometric coordinates for all diastereomeric transition states can be found in the

 ©ARKAT-USA, Inc.

Supplemental Materials. Notably, the lowest transition states had the *trans*-2-substituted cyclohexanol configured with both substituents in the axial position for (±)-**2**.

The LUMO was found to be localized almost entirely in the pyridinium ring for the catalyzed reaction in all cases. In the catalyzed reaction, there appears to be an interaction of either the heteroatom or the aromatic moiety on the *trans*-2-substituent with the pyridinium ring, on which the LUMO is localized, causing the *trans*-2-substituent to be in close vicinity. This is not the case for (±)-**13**, where both heteroatom and aromatic moiety are absent. As a result, no clear preference in conformation of the transition state was observed. This interaction is also notably absent in the uncatalyzed reaction and no such interaction could be inferred between the heteroatom or the aromatic moiety and the chlorine leaving group for (±)-**2**. These computations suggest that the presence of a heteroatom and/or aromatic moiety on the *trans*-2-substituent of cyclohexanol causes it to interact favorably with the pyridinum species in the transition state. This overall change in conformation from the uncatalyzed to the catalyzed reaction for (±)-**2** may be the reason for the observed reversal in diastereoselectivity.

Conclusions

After optimization of the catalytic reaction conditions, using auxiliary base to overcome the catalyst-load dependence on the *dr*, thirteen racemic *trans*-2-substituted alcohols were screened with two racemic acyl chlorides for reversal of *dr*. Highest *dr* was found with cyclohexyloxy-substituted (±)-**8** in the case of the uncatalyzed reaction with (±)-**15** (*dr* 1:10) and in the pyridine-catalyzed reaction with the tolylsulfonyl-containing compound (±)-**11** with (±)-**14** (*dr* 15:1). Stereoselectivity was generally higher with the less sterically demanding acyl chloride (±)-**14**as opposed to (±)-**15**. The heteroatom on the *trans*-2-substituent appears to be essential for the reversal of *dr* to be observed. Computational modeling of the reaction points to the importance of the heteroatom and/or aromatic moiety on the *trans*-2-substituent, as well. With further improvements to the *dr*, especially through modification close to the alcohol functionality of the cyclohexanols substrate, this method may provide valuable in the stereodivergent resolution of racemic acyl chlorides.

Experimental Section

General. Sodium borate was purchased from EMScience, Copper (II) tetrafluoroborate from Alfa Aesar, Naphthanol from Matheson Coleman & Bell and Phenol from Mallinckrodt. All other reagents were obtained from Sigma-Aldrich and used without further purifications. Solvents were distilled prior to use. Column chromatography was performed on silica gel (Sorbent Technologies, 40-75 μm) and fractions analyzed with TLC run on equivalent mobile phase and analyzed through UV or charring with H_2SO_4/MeOH. Melting points were determined

 ©ARKAT-USA, Inc.

using a Stanford Research Systems Digimelt MPA160. ^{1}H-NMR and ^{13}C-NMR spectra were acquired on a JEOL ECA-600 NMR-spectrometer (600 and 150 MHz, respectively). Structural assignments were corroborated by homonuclear and heteronuclear 2D NMR methods (COSY, HMQC, HMBC and TOCSY where necessary). Accurate mass measurements were performed on a JEOL Direct Analysis in Real Time (DART) Mass Spectrometer with AccuTOF mass analyzer (Peabody, MA, USA) with polyethyleneglycol as an internal calibrant. Samples were ionized directly from a drop of solution on the tip of a glass capillary under ambient conditions without sample preparation. ^{1}H and ^{13}C NMR spectra and DART-MS spectra of all compounds are supplied in the Supplemental Material.

Synthesis of (±)-*trans*-2-substituted cyclohexanols.

Compound (±)-**1 [(±)-*trans*-2-(*p*-tolylsulfanyl)cyclohexanol].** To a solution of cyclohexene oxide (9.88 g, 101 mmol) in 50 mL THF was added 13.5 g of *p*-thiocresol (109 mmol), 4 g of borax (10.5 mmol) and 50 mL of water. The reaction mixture was heated to 50 °C and stirred for 2 hours. Then, THF was evaporated off and 150 mL of 5% NaOH soln. (w/v) were added and stirred for 30 min. The mixture was extracted with CH_2Cl_2 (4x75 mL) and the extracts were combined and dried over Na_2SO_4. Filtration and evaporation of the solvent yielded a yellow viscous liquid that crystallized at 4 ºC overnight. The crude product was recrystallized from hexane to give the product as a white crystalline solid (20.3 g, 91%). mp 45-47 ºC. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.35 (dt, 1.8 Hz, 7.8 Hz, 2H, Ar), 7.10 (br d, 7.8 Hz, 2H, Ar), 3.27 (dt, 4.2 Hz, 9.6 Hz, H-1), 3.04 (broad s, 1H, OH), 2.66 (ddd, 4.2 Hz, 10.2 Hz, 12.0 Hz, H-2), 2.33 (s, 3H, Tolyl-CH_3), 2.07 (m, 2H, CH_2), 1.66 (m, 2H, CH_2), 1.26 (m, 4H,CH_2). ^{13}C NMR (150 MHz, $CDCl_3$): δ 138.28 (Ar-C_q), 134.83 (Ar-CH), 134.60 (Ar-CH), 129.94 (Ar-CH), 129.64 (Ar-CH), 128.33 (Ar-C_q), 71.70 (C1), 56.58 (C2), 33.66 (C6), 32.45 (C3), 26.12 (C5), 24.22 (C4), 21.05 (tolyl-CH_3). HRMS: *m/z* calculated for $C_{13}H_{19}OS$ $[M + H]^+$ 223.1152, found 223.1161; *m/z* calculated for $C_{13}H_{19}OS$ $[M + H - H_2O]^+$ 205.1056, found 205.1042.

Compound (±)-**2 [(±)-*trans*-2-(*p*-tolyloxy)cyclohexanol].** To 50 mL of a 0.5 M solution of Na in absoluted ethanol was added cyclohexene oxide (5.0 mL, 49.4 mmol) and *p*-cresol (5.36 g, 49.6 mmol) with stirring and the reaction was heated to 80 ºC with stirring for 24 hours. The yellow solution was then cooled, quenched with 10 mL H_2O and neutralized using conc. HCl acid. The solution was then diluted with 50 mL of CH_2Cl_2 and transferred to a separatory funnel. The organic layer was separated and the aqueous layer washed with CH_2Cl_2 (20 mL). The combined organic layers (yellowish liquid) were washed with H_2O (30 mL) and sat. NaCl solution (30 mL) consecutively and then dried over Na_2SO_4. The drying agent was filtered off and the solvent evaporated to give 10.02 g of a tan solid. The crude product was recrystallized from hexane and combined with a second crop of crystals from the filtrate to yield 7.24 g (35.1 mmol, 71%) of white needle-like crystals. mp 84-87 ºC. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.08 (m, 2H, Ar), 6.85 (dt, 2.7 Hz, 8.4 Hz, 2H, Ar), 3.93 (ddd, 4.2 Hz, 8.4 Hz, 10.2 Hz, H-1), 3.70 (ddd, 4.8 Hz, 8.4 Hz, 10.8 Hz, H-2), 2.43 (broad s, 1H, OH), 2.29 (s, 3H, Tolyl-CH_3), 2.11 (m, 2H, CH2), 1.74 (m, 2H, CH_2), 1.33 (m, 4H, CH_2). ^{13}C NMR (150 MHz, $CDCl_3$): δ 155.78 (Ar-C_q),

 ©ARKAT-USA, Inc.

130.67 (Ar-C_q), 130.78 (2C, Ar-CH), 116.62 (2C, Ar-CH), 82.75 (C-1), 73.61 (C-2), 32.12, 29.34, 24.40, 24.01, 20.55 (tolyl-CH_3). HRMS: *m/z* calculated for $C_{13}H_{19}O_2$ $[M + H]^+$ 207.1380, found 207.1373, *m/z* calculated for $C_{13}H_{17}O$ $[M + H - H_2O]^+$ 189.1284, found 189.1278.

Compound (±)-**3 [(±)-*trans*-2-(phenyloxy)cyclohexanol].** To 10 mL of a roughly 0.4 M solution of Na in ethanol was added cyclohexene oxide (1.0 mL, 9.9 mmol) and phenol (0.93 g, 10.2 mmol) with stirring and the reaction mixture was heated to gentle reflux with continued stirring for 24 hours. The solution was then cooled and quenched with 10 mL water. Then, it was neutralized using conc. HCl acid. The yellow liquid was then diluted with 10 mL of CH_2Cl_2 and transferred to a separatory funnel. The organic layer was separated and the aqueous layer washed with CH_2Cl_2 (2 x 10 mL). The combined organic layers (yellow liquid) were washed with 15 mL sat. NaCl solution and dried over Na_2SO_4. The drying agent was filtered off and the solvent evaporated to give an off-white to yellow solid. The crude product was recrystallized from hexane to yield 0.89 g (4.6 mmol, 47%) of fine white crystals. mp 83-84 ºC. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.27 (m, 2H, Ar), 6.95 (m, 3H, Ar), 3.99 (ddd, 4.2 Hz, 8.4 Hz, 10.2 Hz, H-1), 3.71 (ddd, 4.8 Hz, 8.4 Hz, 10.8 Hz, H-2), 2.60 (broad s, 1H, OH), 2.15 (m, 1H, H-6a), 2.10 (m, 1H, H-3a), 1.74 (m, 2H, CH_2), 1.43-1.24 (m, 4H, CH_2). ^{13}C NMR (150 MHz, $CDCl_3$): δ 157.93(Ar-C_q), 129.64 (2C, Ar-CH), 121.36 (1C, Ar), 116.45 (2C, Ar-CH), 82.29 (C-1), 73.55 (C-2), 32.12 (C-3), 29.28 (C-6), 24.09, 24.02. HRMS: *m/z* calculated for $C_{12}H_{17}O_2$ $[M + H]^+$ 193.1224, found 193.1245, *m/z* calculated for $C_{12}H_{15}O$ $[M + H - H_2O]^+$ 175.1118, found 175.1150.

Compound (±)-**4 [(±)-*trans*-2-(napthalen-2-yloxy)cyclohexanol].** In a 100 mL round-bottom flask equipped with reflux condenser was placed a previously prepared solution of NaOH in ethanol (pH 14, 18 mL) to which was added cyclohexene oxide (2.0 mL, 20.0 mmol) and 2-naphthanol (2.95 g, 20.5 mmol). The sandcolored suspension was stirred and heated to about 90 ºC (oil bath temperature), which caused 2-naphthanol to dissolve and gave a clear brown solution. Reaction progress was monitored *via* TLC (CH_2Cl_2). After consumption of starting material, solution was allowed to cool to give a light-brown to yellow solution with off-white solid. The suspension was then diluted with 5 mL water and neutralized using conc. HCl. The product was then extracted using 20 mL CH_2Cl_2 and the aqueous layer washed twice with 10 mL CH_2Cl_2. The organic layers were combined and dried over Na_2SO_4. After filtering off the drying agent, solvent was removed to give a sandcolored solid, which was recrystallized from ethanol to yield the product as fine white needle-shaped crystals (2.48 g, 52 %). mp 136-137 ºC. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.74 (t, 6.6 Hz, 2H, Ar), 7.40 (d, 8.4 Hz, 1H, Ar), 7.42 (ddd, 1.2 Hz, 6.6 Hz, 7.8Hz, 1H, Ar), 7.32 (ddd, 1.2 Hz, 6.6 Hz, 7.8 Hz, 1H, Ar), 7.21 (br d, 2.4 Hz, 1H, Ar), 7.15 (dd, 2.4 Hz, 9.0 Hz, 1H, Ar), 4.15 (ddd, 4.8 Hz, 9.0 Hz, 10.8 Hz, H-1), 3.77 (ddd, 4.8 Hz, 8.4 Hz, 10.8 Hz, H-2), 2.24 (m, 1H, H-6), 2.12 (m, 1H, H-3), 2.00 (br s, OH), 1.77 (m, 2H, CH_2), 1.44 (m, 1H, CH_2), 1.40-1.29 (m, 3H, CH_2). ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 155.78 (Ar, **C**-O, C-7), 134.58 (Ar, C_q), 129.65 (Ar, CH), 129.31 (Ar, C_q), 127.70 (Ar, CH), 126.84 (Ar, CH), 126.47 (Ar, CH), 123.91 (Ar, CH), 119.66 (Ar, CH), 109.58 (Ar, CH), 82.36 (C-1), 73.55 (C-2), 32.20 (C-3), 29.20 (C-6), 24.10 (C-4), 24.01 (C-5). HRMS: *m/z* calculated for

 ©ARKAT-USA, Inc.

$C_{16}H_{19}O_2$ $[M + H]^+$ 243.1380, found 243.1409. *m/z* calculated for $C_{16}H_{17}O$ $[M + H - H_2O]^+$ 225.1285, found 225.1278.

Compound (±)-5 [(±)-*trans*-2-(3,4,5-trimethoxyphenyloxy)cyclohexanol]. In a 100 mL round-bottom flask added 1.50 mL cyclohexene oxide (14.8 mmol) and 2.69 g of 3,4,5-trimethoxyphenol (14.6 mmol) in 20 mL of previously prepared NaOH in EtOH solution (pH = 14). A reflux condenser was attached and the reaction heated to reflux using an oilbath. The dark brown solution was heated for 6 hours, then allowed to cool to RT. The solution was diluted with 15 mL H_2O and then extracted using 30 mL of CH_2Cl_2. The aqueous layer was washed twice more using 10 mL of CH_2Cl_2 each and the combined organic layers were dried over Na_2SO_4. The drying agent was filtered off and solvent removed using a rotavap to give a brown viscous oil which solidified after cooling. The crude product was recrystallized from hexane to yield off-white to tan crystals (3.38 g, 81%). mp 76-81 ºC. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 6.19 (s, 2H, Ar), 3.90 (m, H-2), 3.82 (s, 6H, -OCH_3), 3.77 (s, 3H, -OCH_3), 3.68 (m, H-1), 2.59 (br s, OH), 2.10 (m, 2H, CH_2), 1.74 (m, 2H, CH_2), 1.38 (m, 1H, CH_2), 1.29 (m, 3H, CH_2). ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 154.47 (Ar-**C**OC_{Cy}), 153.80 (2 C, Ar-**C**OCH_3), 132.97 (Ar-**C**OCH_3), 94.68 (2 C, Ar-CH), 83.25 (C-2), 73.57 (C-1), 61.10 (-OCH_3), 56.22 (2 C, -OCH_3), 32.15 (CH_2), 29.54 (CH_2), 24.09 (CH_2), 23.97 (CH_2). HRMS: *m/z* calculated for $C_{15}H_{23}O_5$ $[M + H]^+$ 283.1540, found 283.1535.

Compound (±)-6 [(±)-*trans*-2-(*p*-*tert*-butyl-phenyloxy)cyclohexanol]. In a 100 mL round-bottom flask equipped with reflux condenser was placed a previously prepared solution of Na in ethanol (0.5 M, 20 mL) to which was added cyclohexene oxide (2.0 mL, 19.8 mmol) and *p*-*tert*-butylphenol (3.21 g, 21.4 mmol). The reaction mixture was heated to about 90 ºC (oil bath temperature), giving a clear solution. Reaction progress was monitored *via* TLC (CH_2Cl_2) and DART-HRMS. After consumption of starting material (165 min), solution was allowed to cool to give a light-yellow solution. The solution was then diluted with 10 mL water and neutralized using conc. HCl, during which a white solid precipitated out. Then, 20 mL CH_2Cl_2 was added to extract the product, giving two opaque colorless layers and the organic layer was separated. The aqueous layer was extracted twice with 12.5 mL CH_2Cl_2. The organic layers were combined and dried over Na_2SO_4. After filtering off the drying agent, solvent was removed to give an off-white solid. The crude product was recrystallized twice from hexane to yield the product as fine white needle-shaped crystals (1.12 g, 23 %). mp 88-91 ºC. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.28 (m, 2H, Ar), 6.87 (m, 2H, Ar), 3.95 (ddd, 4.8 Hz/9.0 Hz/10.2 Hz, 1H, H-2), 3.69 (m, 1H, H-1), 2.60 (br s, OH), 2.15 (m, 1H, CH_2), 2.09 (m, 1H, CH_2), 1.73 (m, 2H, CH_2), 1.42-1.24 (m, 4H, CH_2), 1.28 (s, 9H, tBu-CH_3). ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 155.62 (Ar, C_q), 144.14 (Ar, C_q), 126.42 (2C, Ar), 115.92 (2C, Ar), 82.43 (C-2), 73.61 (C-1), 34.18 (C_q, tBu), 32.09, 31.59 (3C, tBu), 29.40, 24.12, 24.03. HRMS: *m/z* calculated for $C_{16}H_{25}O_2$ $[M + H]^+$ 249.1850, found 249.1835; *m/z* calculated for $C_{16}H_{23}O$ $[M + H - H_2O]^+$ 231.1744, found 231.1716; *m/z* calculated for $C_{32}H_{49}O_4$ $[2M + H]^+$ 497.3626, found 497.3634; *m/z* calculated for $C_{16}H_{24}O_2$ $[M]^{+\bullet}$ 248.1776, found 248.1736.

 ©ARKAT-USA, Inc.

Compound (±)-**7 [(±)-*trans*-2-(2,6-dimethylphenyloxy)cyclohexanol].** To a solution of Na (0.1 g) in ethanol (10 mL) was added cyclohexene oxide (1.0 mL, 9.9 mmol) and 2,6-dimethylphenol (1.25 g, 10.2 mmol) with stirring and the reaction mixture was heated to gentle reflux for 24 hours. The solution was then cooled and quenched with 10 mL water. Then, it was neutralized using conc. HCl acid. The dark-brown liquid was then diluted with 10 mL of CH_2Cl_2 and transferred to a separatory funnel. The organic layer was separated and the aqueous layer washed with CH_2Cl_2 (2 x 10 mL) until a nearly clear yellow aqueous layer remained. The combined organic layers (dark-brown liquid) were washed with 15 mL sat. NaCl solution and dried over Na_2SO_4. The drying agent was filtered off and the solvent evaporated to give a dark-brown liquid (2.0 g). The crude product was purified via column chromatography (mob phase 90:10 hexane:ethyl acetate) to yield 1.52 g (6.9 mmol, 80%) of a clear pale-yellow liquid (R_f = 0.30). ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.99 (d, 7.8 Hz, 2H, *m*-Ar), 6.90 (dd, 7.2 Hz, 8.4 Hz, 1H, *p*-Ar), 3.79 (m, 2H, H-1, H-2), 2.99 (broad s, 1H, OH), 2.29 (s, 6H, CH_3), 2.09 (m, 1H), 1.76 (m, 1H), 1.68 (m, 2H), 1.4-1.25 (m, 3H), 1.11 (tq, 3.6 Hz, 13.2 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 153.33 ($C_{q,Ar}$-O-C), 131.41 (2C, C_q), 129.09 (2C, *m*-Ar-CH), 123.65 (1C, *p*-Ar-CH), 84.81, 74.62, 32.25, 29.70, 24.34, 24.13, 17.49 (2C, CH_3). HRMS: *m/z* calculated for $C_{14}H_{21}O_2$ $[M + H]^+$ 221.1537, found 221.1513, *m/z* calculated for $C_{14}H_{19}O$ $[M + H - H_2O]^+$ 203.1431, found 203.1440; found 221.1513, *m/z* calculated for C14H_{24}NO2 $[M + NH_4]^+$ 238.1807, found 238.1846.

Compound (±)-**8 [(±)-*trans*-2-(cyclohexyloxy)cyclohexanol].** In a 100 mL round-bottom flask equipped with reflux condenser was placed a previously prepared solution of Na in cyclohexanol (0.5 M, 20 mL) to which was added cyclohexene oxide (2.0 mL, 19.8 mmol). The reaction mixture was heated to reflux. Reaction progress was monitored *via* TLC (CH_2Cl_2). After 24 h, solution was allowed to cool and was then diluted with 20 mL water and neutralized using conc. HCl. Then, 10 mL CH_2Cl_2 was added to extract the product and the sandcolored organic layer was separated. The brown-orange colored aqueous layer was extracted twice with 15 mL CH_2Cl_2. The organic layers were combined and washed with 20 mL water, then 2 x 20 mL sat. NaCl solution and consequently dried over Na_2SO_4. After filtering off the drying agent, solvent was removed using rotavap to give a yellow liquid, from which cyclohexanol was removed using a rotavap and oil pump vacuum. The remaining yellow oily liquid was separated using column chromatography (mob. phase CH_2Cl_2) to give the desired product (R_f = 0.18) as a clear yellow oil (640.4 mg, 16 %). ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 3.34 (m, 2H, H-1, H-7), 3.08 (dt, 4.2 Hz, 10.2 Hz, 1H, H-2), 2.70 (broad s, OH), 2.0-1.9 (m, 3H), 1.82 (m, 1H), 1.68 (m, 4H), 1.51 (m, 1H), 1.3-1.1 (m, 10H). ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 81.39 (C-2), 75.90 (C-7), 73.82 (C-1), 34.22, 32.60, 32.03, 30.63, 25.76, 24.53, 24.51, 24.37, 24.09. HRMS: *m/z* calculated for $C_{12}H_{23}O_2$ $[M + H]^+$ 199.1693, found 199.1692. *m/z* calculated for $C_{12}H_{21}O$ $[M + H - H_2O]^+$ 181.1587, found 181.1615.

Compound (±)-**9 [*trans*-2-(*t*-butoxy)cyclohexanol].** In a 100 mL RBF was combined 61.8 mg (0.26 mmol) of $Cu(BF_4)_2$ in 20 mL dichloromethane and added 2.0 mL (19.8 mmol) of cyclohexene oxide and 7.6 mL (79.5 mmol) of freshly distilled *tert*-butanol and the pale blue

 ©ARKAT-USA, Inc.

solution stirred at rt. After the starting material was consumed (monitored by TLC, 90:10 hexane:ethyl acetate) after ~24 h, the reaction was quenched with 20 mL of water, the layers separated and the aqueous extracted with 2x7 mL of dichloromethane. The combined org. layers were washed with 2x20 mL sat. NaCl soln. and dried over Na_2SO_4. The drying agent was then filtered off and solvent evaporated to give a slightly milky liquid. TLC and DART-MS analysis showed the formation of multiple products (including a dimeric compound containing two cyclohexane rings). The desired product was isolated using column chromatography to give a clear viscous oil that solidified to form white needle-like crystals overnight at 4 ºC (0.60 g, 18% yield). m.p. 32-34 ºC. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 3.30 (m, 1H, H-1), 3.19 (m, 1H, H-2), 2.55 (s, OH), 2.01 (m, 1H, H-6a), 1.90 (m, 1H, H-3a), 1.66 (m, 1H, H-4a), 1.65 (s, 1H, H-5a), 1.30-1.22 (m, 4H, H-3b,4b,5b,6b), 1.22 (s, 9H, CH_3). ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 76.57 (C-2), 74.08 (C-1), 73.97 (C_q, *t*Bu), 33.51 (C-3), 32.17 (C-6), 29.16 (3C, CH_3), 24.82 (C-5), 24.27 (C-4). HRMS: *m/z* calculated for $C_{10}H_{21}O_2$ $[M + H]^+$ 173.1537, found 173.1525.

Compound (±)-**10 [(±)-*trans*-2-(pyridin-2-ylthio)cyclohexanol].** In a 50 mL round-bottom flask equipped with a reflux condenser was placed 2-mercaptopyridine (1.22 g, 11.0 mmol) in a 1:1 mixture of THF:H_2O (10 mL) and added cyclohexene oxide (1.0 mL, 9.9 mmol) and sodium tetraborate (0.43 g, 1.1 mmol). The reaction mixture was heated to about 40 ºC, giving a yellow solution. After 2.5 h, the solution was allowed to cool and then extracted with 3x10 mL CH_2Cl_2. The combined yellow organic layers were washed with sat. $NaHCO_3$ soln. (15 mL) and dried over Na_2SO_4. After filtering off the drying agent, solvent was removed to give a yellow oil, which was purified using column chromatography (silica, 99:1 CH_2Cl_2:MeOH, R_f 0.18) to give a clear yellow oil (0.68 g, 33%). ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 8.33 (m, 1H, H-11), 7.48 (t, 6.9 Hz, 1H, H-9), 7.27 (dd, 0.6 Hz, 7.8 Hz, H-8), 7.00 (m, H-10), 6.12 (s, 1H, OH), 3.50 (dt, 4.2 Hz, 10.2 Hz, H-2), 3.40 (dt, 3.9 Hz, 11.4 Hz, H-1), 2.19 (br d, 12.6 Hz, H-3a), 2.12 (br d, 13.2 Hz, H-6a), 1.74 (d, 6.6 Hz, 2H, H-4a,5a), 1.46 (br q, 12.6 Hz, H-6b), 1.37 (br q, 12.0 Hz, H-3b), 1.28 (q, 12.0 Hz, 2H, H4b,5b). ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 159.60 (C_q, C-7), 148.76 (C-11), 136.67 (C-9), 123.43 (C-8), 120.16 (C-10), 76.07 (C-2), 52.39 (C-1), 36.28 (C-3), 32.49 (C-6), 26.37, 24.25. HRMS: *m/z* calculated for $C_{11}H_{16}NSO$ $[M + H]^+$ 210.0948, found 210.0973. *m/z* calculated for $C_{11}H_{14}NS$ $[M + H - H_2O]^+$ 192.0842, found 192.0798.

Compound (±)-**11 [(±)-*trans*-2-(*p*-tolylsulfonyl)cyclohexanol].** (Adapted from [15].) In a 50 mL round-bottom flask with a condenser attached, was placed 1.99g of *trans*-2-(p-tolylsulfanyl)cyclohexanol (8.97 mmol) and 4 mL glacial acetic acid. 4 mL of hydrogen peroxide (30 wt%, 35.3 mmol) was added and the milky white mixture heated to reflux for 5 hours, after which the condenser was taken off and the clear-yellow solution heated without boiling. After another 1.5 hours, the gold-brown viscous liquid was allowed to cool to RT and left open overnight to solidify and give a tan-colored solid cake, which was recrystallized from a minimum amount of solvent (4:6 mix of $CHCl_3$:hexane) to yield the product as pale-yellow crystals (1.40 g, 61.4%). m.p. 109-116 ºC. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.76 (d, 7.8Hz, 2H, Ar), 7.38 (d, 8.4 Hz, 2H, Ar), 3.88 (dt, 4.8Hz, 10.2 Hz, H-1), 3.83 (s, OH), 2.95 (ddd, 4.2Hz, 10.2Hz, 12.6Hz, H-2), 2.46 (s, 3H, tolyl-CH_3), 2.12 (m, 1H, H-6), 1.89 (m, 1H, H-3), 1.70 (m,

 ©ARKAT-USA, Inc.

2H, CH_2), 1.37-1.12 (m, 4H, H-3,H-6,CH_2). ^{13}C NMR (150 MHz, $CDCl_3$): δ 145.21 (Ar, C_q), 133.78 (Ar, C_q), 129.86 (Ar, 2C), 129.05 (Ar, 2C), 68.98 (C-2), 68.28 (C-1), 34.12 (C-6), 25.75, 24.56 (C-3), 23.58, 21.64 (tolyl-CH_3). HRMS: *m/z* calculated for $C_{13}H_{19}SO_3$ $[M + H]^+$ 255.1050, found 255.1079.

Compound (±)-**12 [(±)-*trans*-2-benzylcyclohexanol].** (Adapted from [16].) In a 50 mL 3-neck flask with condenser, dropping funnel and bubbler attached, placed 0.61 g magnesium ribbon pieces and flushed with N_2. Added 18 mL dry THF, then slowly added 1.2 mL benzyl bromide (in 8 mL dry THF) through the dropping funnel. Cooled on ice, then let stir at RT for 2h. To the slushy gray reaction mixture was added 0.7 mL cyclohexene oxide (in 5 mL THF) dropwise while cooling on ice. After ~15 min, allowed the dark gray colored reaction mixture to stir at rt overnight. Quenched with 20 mL H_2O, then filtered into a separatory funnel and extracted the aqueous with ethyl acetate (3x20 mL). The combined organic layers were washed with 20 mL sat. NaCl solution and then dried over $MgSO_4$. After evaporation of solvent, a pale yellow oil was retained, which was separated via column chromatography (mob. phase gradient 9:1 – 8:2 hexane:ethyl acetate) to isolate the product as white needle-like crystals (78 mg, 6%) after evaporation of eluent (R_f = 0.18, 9:1 hexane:ethyl acetate). mp 73-75 ºC. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.27 (m, 2H), 7.18 (m, 3H), 3.29 (dt, 4.8 Hz, 9.6 Hz, H-1), 3.16 (dt, 13.8 Hz, 5.4 Hz, 1H, Benzyl-CH_2), 2.35 (m, 1H, Benzyl-CH_2), 1.97 (m, 1H), 1.71 (m, 1H), 1.63 (m, 1H), 1.57 (m, 1H), 1.50 (m, 1H, H-2), 1.43 (s, 1H, OH), 1.26 (m, 2H), 1.08 (m, 1H), 0.90 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 140.84 ($C_{q,Ar}$), 129.50 (2C, Ar-CH), 128.26 (2C, Ar-CH), 125.83 (1C, Ar-CH), 74.65 (C-1), 47.13 (C-2), 39.10 (C-7), 35.93, 30.03, 25.51, 24.99. HRMS: *m/z* calculated for $C_{13}H_{19}O$ $[M + H]^+$ 191.1431, found 191.1433, *m/z* calculated for $C_{13}H_{17}$ $[M + H – H_2O]^+$ 173.1325, found 173.1319; *m/z* calculated for $C_{13}H_{22}NO$ $[M + NH_4]^+$ 208.1701, found 208.1712; *m/z* calculated for $C_{26}H_{37}O_2$ $[2M + H]^+$ 381.2789, found 381.2769.

Acylation reactions.

General procedure. Racemic *trans*-2-substituted cyclohexanols (±)-**1-13** (0.2 mmol) were dissolved in 1 mL of solvent (CH_2Cl_2). If applicable, pyridine (0.8 μL, 0.01 mmol) was added immediately afterwards together with one equivalent of ProtonSponge® (21 mg, 0.1 mmol). The reaction was initiated by the addition of (±)-2-chloropropionyl chloride (±)-**14** or (±)-2-chloro-2-phenylacetyl chloride (±)-**15** (0.1 mmol respectively). The reaction mixtures were stirred at rt for 24 hours and then evaporated to remove solvent (N_2 flow). The crude reaction mixtures were then immediately taken up in CDCl3 for ^{1}H NMR analysis. After this, the acylation product of the reactions was isolated via column chromatography (mob. phase hexane:ethyl acetate or CH_2Cl_2, see below) for full characterization.

Compound (±)-**16 [(±)-(*trans*-2-(*p*-tolylsulfanyl)cyclohexyl) 2-chloropropanoate].** Mixture of diastereomers (ratio of diastereomers determined using quartet signals for C**H**(CH_3)Cl at 4.30-4.21 ppm). Isolated via column chromatography (Rf 0.41, 95:5 hexane:ethyl acetate). Clear pale yellow oil. ^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm) 7.30 (m, 2H, Ar), 7.15 (m, 2H, Ar), 4.80 (dt, 4.2 Hz, 9.0 Hz, H-1), 4.30/4.26 (q, 10.2 Hz, 1H, C**H**(CH_3)Cl), 3.10 (*dt*, 4.2 Hz, 9.6 Hz, H-2), 2.32 (s, 3H, tolyl-CH_3), 2.05 (m, 2H, H-3a), 1.70 (m, 2H), 1.67/1.65 (d, 10.2 Hz, 3H,

 ©ARKAT-USA, Inc.

CH(C**H**$_3$)Cl), 1.48-1.38 (m, 2H, H-6a,b), 1.38-1.23 (m, 2H, CH_2, H-3b). ^{13}C NMR (150 MHz, $CDCl_3$): δ 169.47/169.33 (C=O), 137.63/137.61 (Ar-C_q), 133.54/133.45 (Ar, 2C), 130.10/130.05 (Ar-C_q), 129.73/129.70 (Ar, 2C), 76.39/76.26 (C-1), 53.07/52.78 (**C**H(CH_3)Cl), 50.24/50.17 (C-2), 31.58/31.40 (C-6), 30.82/30.55 (C-3), 24.86/24.64, 23.42/23.27 (CH(**C**H_3)Cl), 21.69/21.54, 21.15 (tolyl-CH_3). HRMS: *m/z* calculated for $C_{16}H_{21}ClO_2S$ $[M]^{+\bullet}$ 312.0951, found 312.0935; *m/z* calculated for $C_{13}H_{19}S$ $[M + H - HO_2C\text{-}CH(CH_3)Cl]^+$ 205.1046, found 205.1016.

Compound (±)-**17 [(±)-(*trans*-2-(*p*-tolyloxy)cyclohexyl) 2-chloropropanoate].** Mixture of diastereomers (ratio of diastereomers determined using quartet signals for C**H**(CH_3)Cl at 4.30-4.26 ppm). Isolated via column chromatography (Rf 0.37, 95:5 hexane:ethyl acetate). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.06 (m, 2H, Ar), 6.84 (m, 2H, Ar), 5.02 (ddd, 4.2 Hz, 7.8 Hz, 9.6 Hz, H-1), 4.30/4.26 (q, 7.2 Hz, C**H**(CH_3)Cl), 4.19 (ddd, 4.2 Hz, 7.8 Hz, 9.0 Hz, H-2), 2.27 (s, 3H, tolyl-CH_3), 2.10 (m, 2H), 1.76 (m, 2H), 1.59/1.56 (d, 7.2 Hz, 3H, CH(C**H$_3$**)Cl), 1.55-1.24 (m, 4H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 169.70 (C=O), 155.99 (Ar-C_q), 130.62 (Ar-C_q), 129.99 (2C, Ar-CH), 116.40 (2C, Ar-CH), 77.53 (C-2), 75.77 (C-1), 52.96 (**C**H(CH_3)Cl), 29.65, 29.30, 23.03, 22.88, 21.58 (CH(**C**H_3)Cl), 20.59 (tolyl-CH_3). HRMS: *m/z* calculated for $C_{16}H_{22}ClO_3$ $[M + H]^+$ 297.1252, found 297.1200, *m/z* calculated for $C_{13}H_{17}O$ $[M + H - HO_2C\text{-}CH(CH_3)Cl]^+$ 189.1284, found 189.1257.

Compound (±)-**18 [(±)-(*trans*-2-(phenyloxy)cyclohexyl 2-chloropropanoate].** Mixture of diastereomers (ratio of diastereomers determined using quartet signals for C**H**(CH_3)Cl at 4.27/4.23 ppm). Isolated via column chromatography (Rf 0.36, 95:5 hexane:ethyl acetate). Clear yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.25 (m, 2H, Ar), 6.93 (m, 3H, Ar), 5.03 (ddd, 4.8 Hz, 8.4 Hz, 9.6 Hz, H-1), 4.27 (m, H-2), 4.27/4.23 (q, 7.2 Hz, C**H**(CH_3)Cl), 2.27 (s, 3H, tolyl-CH_3), 2.10 (m, 2H), 1.76 (m, 2H), 1.57/1.53 (d, 7.2 Hz, 3H, CH(C**H$_3$**)Cl), 1.6-1.2 (m, 4H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 169.56 (C=O), 158.16 (Ar-C_q), 129.56 (2C, Ar-CH), 121.26 (C, Ar-CH), 116.32/116.19 (2C, Ar-CH), 77.13 (C-1), 75.79 (C-2), 52.93 (**C**H(CH_3)Cl), 29.65, 29.32, 23.02, 22.89, 21.54 (CH(**C**H_3)Cl). HRMS: *m/z* calculated for $C_{15}H_{20}ClO_3$ $[M + H]^+$ 283.1096, found 283.1096; *m/z* calculated for $C_{12}H_{15}O$ $[M + H - HO_2C\text{-}CH(CH_3)Cl]^+$ 175.1118, found 175.1113.

Compound (±)-**19 [(±)-(*trans*-2-(napthalen-2-yloxy)cyclohexyl) 2-chloropropanoate].** Mixture of diastereomers (ratio of diastereomers determined using quartet signals for C**H**(CH_3)Cl at 4.30/4.24 ppm). Isolated via column chromatography (Rf 0.28, 95:5 hexane:ethyl acetate). White solid. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.74 (m, 3H, Ar), 7.44 (m, 1H, Ar), 7.34 (m, 1H, Ar), 7.25 (m, 1H, Ar), 7.15 (m, 1H, Ar), 5.12 (m, H-1), 4.45 (dt, 4.2 Hz, 9.0 Hz, 9.0 Hz, H-2), 4.30/4.24 (q, 6.6 Hz, C**H**(CH_3)Cl), 2.25 (m, 1H, H-3a), 2.14 (m, 1H, H-6a), 1.81 (m, 2H), 1.55/1.50 (d, 7.2 Hz, CH(C**H$_3$**)Cl), 1.67-1.38 (m, 4H). ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 169.72/169.59 (C=O), 155.97/155.94 (**C**$_{Ar}$-O-C), 134.56 (Ar-C_q), 129.60 (Ar-CH), 129.26/129.23 (Ar-C_q), 127.71 (Ar-CH), 126.87/126.82 (Ar-CH), 126.49/126.44 (Ar-CH), 123.89/123.86 (Ar-CH), 119.64/119.54 (Ar-CH), 109.13/108.99 (Ar-CH), 77.41 (C-2), 75.99/75.69 (C-1), 52.88/52.76 (**C**H(CH_3)Cl), 29.70/29.59, 29.52/29.38, 23.24/23.13, 23.07/22.93, 21.51/21.48 (CH(**C**H_3)Cl). HRMS: *m/z* calculated for $C_{19}H_{22}ClO_3$ $[M + H]^+$

 ©ARKAT-USA, Inc.

333.1252, found 333.1292; *m/z* calculated for $C_{16}H_{17}O$ [M + H – HO_2C-$CH(CH_3)Cl]^+$ 225.1274, found 225.1276.

Compound (±)-**20 [(±)-(*trans*-2-(3,4,5-trimethoxyphenyloxy)cyclohexanol].** Mixture of diastereomers (ratio of diastereomers determined using quartet signals for C**H**(CH_3)Cl at 4.30/4.27 ppm). Isolated via column chromatography (Rf 0.80, 1:1 hexane:ethyl acetate). Clear colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 6.20/6.19 (s, Ar, 2H), 5.0 (dt, 4.2 Hz, 8.4 Hz, 1H, H-2), 4.30/4.27 (q, 7.2 Hz, 1H, C**H**(CH_3)Cl), 4.18 (m, 1H, H-1), 3.81 (s, 6H, -OCH_3), 3.76 (s, 3H, -OCH_3) 2.06 (m, 2H, CH_2), 1.74 (m, 2H, CH_2), 1.59/1.57 (d, 6.6 Hz, 3H, CH(C**H$_3$**)Cl), 1.52 (m, 1H, CH_2), 1.40 (m, 3H, CH_2). ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 169.60/169.55 (C=O), 154.68/154.62 (**C**-O-C_{Cy}), 153.73 (Ar, 2C, C_q), 132.75 (Ar, C_q), 94.29/94.21 (Ar, 2C, CH), 77.54 (C-1), 75.27 (C-2), 61.06 (-OCH_3), 56.21 (2C, -OCH_3), 52.84/52.72 (**C**H(CH_3)Cl), 29.73/29.60, 29.17/29.00, 22.89/22.71, 22.80/22.61, 21.54/21.47 (CH(**C**H_3)Cl). HRMS: *m/z* calculated for $C_{18}H_{26}ClO_6$ $[M + H]^+$ 373.1413, found 373.1453.

Compound (±)-**21 [(±)-(*trans*-2-(*p-tert*-butyl-phenyloxy)cyclohexyl 2-chloropropanoate].** Mixture of diastereomers (ratio of diastereomers determined using quartet signals for C**H**(CH_3)Cl at 4.27/4.24 ppm). Isolated via column chromatography (Rf 0.35, 95:5 hexane:ethyl acetate). ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.26 (m, 2H, Ar), 6.86 (m, 2H, Ar), 5.02 (m, 1H, H-2), 4.27/4.24 (q, 6.6 Hz, 1H, C**H**(CH_3)Cl), 4.23 (m, 1H, H-1), 2.13 (m, 1H, CH_2), 2.07 (m, 1H, CH_2), 1.75 (m, 2H, CH_2), 1.56/1.53 (d, 6.6 Hz, 3H, CH(C**H$_3$**)Cl), 1.55-1.25 (m, 4H, CH_2), 1.28 (s, 9H, tBu-CH_3). ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 169.56 (C=O), 155.86 (C_q, Ar), 144.00 (C_q, Ar), 126.31 (Ar, 2C, CH), 115.87 (Ar, 2C, CH), 115.72 (Ar, C_q), 77.12 (C-1), 75.81 (C-2), 52.98 (**C**H(CH_3)Cl), 34.17 (C_q, tBu), 31.60 (tBu-CH_3), 29.66, 29.30, 22.99, 22.86, 21.55 (CH(**C**H_3)Cl). HRMS: *m/z* calculated for $C_{19}H_{28}ClO_3$ $[M + H]^+$ 339.1722, found 339.1691; *m/z* calculated for $C_{16}H_{23}O$ [M + H – HO_2C-$CH(CH_3)Cl]^+$ 231.1744, found 231.1729.

Compound (±)-**22 [(±)-(*trans*-2-(2,6-dimethylphenyloxy)cyclohexyl 2-chloropropanoate].** Mixture of diastereomers (ratio of diastereomers determined using quartet signals for C**H**(CH_3)Cl at 4.29/4.24 ppm). Isolated via column chromatography (Rf 0.61, 9:1 hexane:ethyl acetate). Clear yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 6.97 (d, 7.2 Hz, 2H, *m*-Ar), 6.88 (t, 7.2 Hz, 1H, *p*-Ar), 5.06 (m, H-1), 4.29/4.24 (q, 7.2 Hz, C**H**(CH_3)Cl), 4.01 (ddd, 4.5 Hz, 8.4 Hz, 10.2 Hz, 1H, H-2), 2.28/2.27 (s, 6H, CH_3), 2.12 (m, 1H), 1.95 (m, 1H), 1.72 (m, 2H), 1.63/1.62 (d, 7.2 Hz, 3H, CH(C**H$_3$**)Cl), 1.52 (m, 1H), 1.40 (m, 2H), 1.21 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 169.56 (C=O), 154.17 (Ar-C_q), 131.07 (2C, Ar-C_q), 129.04 (2C, Ar-CH), 123.43 (Ar-CH), 80.12 (C-2), 77.49 (C-1), 53.13 (**C**H(CH_3)Cl), 30.32, 29.91, 23.50 (2C), 21.73 (CH(**C**H_3)Cl), 17.36 (2C, CH_3). HRMS: *m/z* calculated for $C_{17}H_{24}ClO_3$ $[M + H]^+$ 311.1409, found 311.1397; *m/z* calculated for $C_{14}H_{19}O$ [M + H – HO_2C-$CH(CH_3)Cl]^+$ 203.1431, found 203.1441; *m/z* calculated for $C_{17}H_{27}ClNO_3$ $[M + NH_4]^+$ 328.1679, found 328.1677.

Compound (±)-**23 [(±)-(*trans*-2-(cyclohexyloxy)cyclohexyl 2-chloropropanoate].** Mixture of diastereomers (ratio of diastereomers determined using quartet signals for C**H**(CH_3)Cl at 4.37/4.36 ppm). Isolated via column chromatography (Rf 0.42, CH_2Cl_2). Clear colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 4.72 (ddd, 4.2 Hz, 8.4 Hz, 9.6 Hz, 1H, H-2), 4.37/4.36 (q, 7.2

 ©ARKAT-USA, Inc.

Hz, 1H, C**H**(CH_3)Cl), 3.35 (m, 2H, H-1, H-7), 2.01 (m, 1H), 1.95 (m, 1H), 1.81 (m, 2H), 1.69 (m, 3H), 1.68 (d, 7.2 Hz, 3H, CH(C**H$_3$**)Cl), 1.65 (m, 1H), 1.50 (m, 1H), 1.4-1.1 (m, 9H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 169.56/169.48 (C=O), 77.54 (C-2), 77.04, 76.60, 52.99 (**C**H(CH_3)Cl), 33.46, 32.87, 31.52, 29.76, 25.81, 24.32, 24.29, 23.57, 23.41, 21.70/21.66 (CH(**C**H_3)Cl). HRMS: *m/z* calculated for $C_{15}H_{26}ClO_3$ $[M + H]^+$ 289.1565, found 289.1553; *m/z* calculated for $C_9H_{16}ClO_3$ $[M + H - C_6H_{10}]^+$ 207.0783, found 207.0774; *m/z* calculated for $C_{12}H_{21}O$ $[M + H - HO_2C\text{-}CH(CH_3)Cl]^+$ 181.1587, found 181.1569.

Compound (±)-**24 [(±)-(*trans*-2-(*tert*-butoxy)cyclohexyl 2-chloropropanoate].** Mixture of diastereomers (ratio of diastereomers determined using quartet signals for C**H**(CH_3)Cl at 4.36/4.34 ppm). Isolated via column chromatography (Rf 0.23, 95:5 hexane:ethyl acetate). Clear pale yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 4.64 (ddt, 4.2 Hz, 9.0 Hz, 9.0 Hz), 4.36/4.34 (q, 6.6 Hz, C**H**(CH_3)Cl), 3.48 (m, 1H), 2.01 (m, 1H), 1.86 (m, 1H), 1.7-1.6 (m, 2H), 1.69/1.68 (d, 7.2 Hz, 3H, CH(C**H$_3$**)Cl), 1.4-1.2 (m, 4H), 1.18/1.17 (9H, tBu). ^{13}C NMR (150 MHz, $CDCl_3$): δ 169.59 (C=O), 76.97, 73.93, 70.41, 53.05/52.76, 32.98, 29.43, 28.79/28.72, 23.12, 23.06, 21.89/21.52 (CH(**C**H_3)Cl). HRMS: *m/z* calculated for $C_{13}H_{24}ClO_3$ $[M + H]^+$ 263.1409, found 263.1426; *m/z* calculated for $C_{10}H_{19}O$ $[M + H - C_4H_8]^+$ 207.0783, found 207.0774.

Compound (±)-**25** [**(±)-*trans*-2-(pyridin-2-ylthio)cyclohexyl 2-chloropropanoate**]. Mixture of diastereomers (ratio of diastereomers determined using quartet signals for C**H**(CH_3)Cl at 4.18/4.17 ppm). Isolated via column chromatography (Rf 0.32, CH_2Cl_2). Clear yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 8.41 (m, 1H, H-14), 7.45 (tt, 2.1 Hz, 7.5 Hz, 1H, H-12), 7.16 (t, 8.4 Hz, 1H, H-11), 6.97 (dd, 5.1 Hz, 7.5 Hz, 1H, H-13), 4.91 (m, 1H), 4.18/4.17 (q, 6.9 Hz, C**H**(CH_3)Cl), 4.11/4.08 (dt, 4.2 Hz, 9.6 Hz, 1H), 2.25 (m, 1H), 2.08 (m, 1H), 1.77 (m, 1H), 1.71 (m, 1H), 1.65 (m, 2H), 1.52/1.51 (d, 7.2 Hz, 3H, CH(C**H$_3$**)Cl), 1.45 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 169.51/169.37 (C_q, C=O), 158.34 (C_q, C-10), 149.52/149.49 (C-14), 136.14/136.11 (H-12), 123.04/122.96 (H-11), 119.77 (H-13), 76.42/76.26, 53.00/52.80 (**C**H(CH_3)Cl), 45.77/45.61, 31.71/31.50, 30.83/30.68, 24.93/24.84, 23.38/23.31, 21.51/21.45 (CH(**C**H_3)Cl). HRMS: *m/z* calculated for $C_{14}H_{19}ClNSO_2$ $[M + H]^+$ 300.0820, found 300.0802. *m/z* calculated for $C_{11}H_{15}NS$ $[M + H - HO_2C\text{-}CH(CH_3)Cl]^+$ 192.0842, found 192.0798.

Compound (±)-**26 [(±)-(*trans*-2-(*p*-tolylsulfonyl)cyclohexyl 2-chloropropanoate].** Mixture of diastereomers (ratio of diastereomers determined using quartet signals for C**H**(CH_3)Cl at 4.03/4.00 ppm). Isolated via column chromatography (Rf 0.39, 8:2 hexane:ethyl acetate). Off-white solid. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.73 (d, 8.4 Hz, 2H), 7.36 (d, 7.8 Hz, 2H), 5.06 (dt, 4.8 Hz, 10.2 Hz, H-1), 4.03/4.00 (q, 7.2 Hz, C**H**(CH_3)Cl), 3.27 (ddd, 4.2 Hz, 9.6 Hz, 12.0 Hz, H-2), 2.44 (s, 3H, tolyl-CH_3), 2.21 (m, 1H), 2.11 (m, 1H), 1.84 (m, 1H), 1.73 (m, 1H), 1.59 (d, 7.2 Hz, 3H, CH(C**H$_3$**)Cl), 1.52 (m, 1H), 1.4-1.2 (m, 3H).^{13}C NMR (150 MHz, $CDCl_3$): δ 168.84 (C=O), 144.91 ($C_{q,Ar}$-S), 135.59 (C_q), 129.94 (2C, Ar), 128.87 (2C, Ar), 71.78 (C-1), 65.32 (C-2), 53.03 (**C**H(CH_3)Cl), 31.05 (C-6), 25.16 (C-3), 23.98, 23.16, 21.74 (CH(**C**H_3)Cl), 21.65. HRMS: *m/z* calculated for $C_{16}H_{22}ClO_4S$ $[M + H]^+$ 345.0922, found 345.0938.

 ©ARKAT-USA, Inc.

Compound (±)-**27 [(±)-(*trans*-2-benzylcyclohexyl) 2-chloropropanoate].** Mixture of diastereomers (ratio of diastereomers determined using quartet signals for C**H**(CH_3)Cl at 4.28/4.23 ppm). Isolated via column chromatography (Rf 0.44, 95:5 hexane:ethyl acetate). Clear colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.21 (m, 2H, Ph), 7.12 (t, 7.8 Hz, 1H, *p*-Ar), 7.06 (m, 2H, Ph), 4.56 (m, 1H, H-1), 4.28/4.23 (q, 6.9 Hz, C**H**(CH_3)Cl), 2.86 (ddd, 3.6 Hz, 13.2 Hz, 29.4 Hz, 1H, H-7a), 2.22 (ddd, 2.4 Hz, 9.0 Hz, 12.0 Hz, H-7b), 1.96 (m, 1H), 1.88-1.65 (m, 6H), 1.65-1.50 (m, 1H), 1.40-0.93 (m, 4H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 169.81 (C=O), 140.16 (Ar-C_q), 129.33/129.28 (2C, Ar-CH), 128.31 (2C, Ar-CH), 126.00 (Ar-CH), 78.73/78.67 (C-1), 52.98/52.88 (**C**H(CH_3)Cl), 43.86/43.66 (C-2), 38.87/38.71 (C-7), 31.58/31.44, 30.02/29.98, 25.01, 24.49, 21.60/21.46 (CH(**C**H_3)Cl). HRMS: *m/z* calculated for $C_{16}H_{22}ClO_2$ $[M + H]^+$ 281.1303, found 281.1303; *m/z* calculated for $C_{13}H_{17}$ $[M + H - HO_2C\text{-}CH(CH_3)Cl]^+$ 173.1325, found 173.1297; *m/z* calculated for $C_{16}H_{25}ClNO_2$ $[M + NH_4]^+$ 298.1564, found 298.1574.

Compound (±)-**28 [(±)-(*trans*-2-methylcyclohexyl) 2-chloropropanoate].** Mixture of diastereomers (ratio of diastereomers determined using doublet signals for CH(C**H$_3$**)Cl at 1.68/1.67 ppm). Isolated via column chromatography (Rf 0.35, 95:5 hexane:ethyl acetate). ^{1}H NMR (600 MHz, $CDCl_3$): δ 4.45 (m, H-1), 4.37/4.36 (q, 7.2 Hz, C**H**(CH_3)Cl), 1.97 (m, 1H), 1.75 (m, 2H), 1.68/1.67 (d, 6.9 Hz, CH(C**H$_3$**)Cl), 1.64-1.55 (m, 2H), 1.35-1.20 (m, 3H), 1.07 (m, 1H), 0.91 (d, 6.6 Hz, 2H, Cy-CH_3), 0.89 (d, 6.6 Hz, 1H, Cy-CH_3). ^{13}C NMR (150 MHz, $CDCl_3$): δ 169.84 (C=O), 80.36/80.24 (C-1), 53.12/52.89 (**C**H$ClCH_3$), 37.31/37.20, 34.74, 33.51, 31.48, 25.35/25.27, 24.68, 21.70/21.48 (CHCl**C**H_3). HRMS: *m/z* calculated for $C_{10}H_{18}ClO_2$ $[M + H]^+$ 205.0990, found 205.1040.

Compound (±)-**29 [(±)-(*trans*-2-(*p*-tolylsulfanyl)cyclohexyl 2-chloro-2-phenylethanoate].** Mixture of diastereomers (ratio of diastereomers determined using signal for H-2 at 3.05/2.99 ppm). Isolated via column chromatography (Rf 0.58, 95:5 hexane:ethyl acetate). Clear pale yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.51/7.42 (m, 2H, Ph), 7.37/7.33 (m, 3H, Ph), 7.32/7.17 (dt, 2.4 Hz, 7.8 Hz, 2H, Tol), 7.12/7.05 (br d, 7.8 Hz, 2H, Tol), 5.31/5.10 (s, 1H, C**H**ClPh), 4.79/4.75 (dt, 4.2 Hz, 8.4 Hz, H-1), 3.05/2.99 (ddd, 4.2 Hz, 9.0 Hz, 10.2 Hz, H-2), 2.34/2.31 (s, 3H, tolyl-CH_3), 2.11/2.05 (m, 1H), 1.93 (m, 1H), 1.65/1.58 (m, 2H), 1.5-1.2 (m, 4H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 167.57 (C=O), 137.67 (C_q), 136.17 (C_q), 133.55 (2C, Tol), 130.26 (C_q), 129.76/129.67 (2C, Tol), 129.30/129.21 (Ph), 128.88/128.80 (2C, Ph), 128.22/127.99 (2C, Ph), 77.38/76.35 (C-1), 59.52/59.37 (**C**HClPh), 50.06 (C-2), 31.33, 30.44, 24.71, 23.20, 21.22 (tolyl-CH_3). HRMS: *m/z* calculated for $C_{21}H_{24}ClSO_2$ $[M + H]^+$ 374.1107, found 374.1101; *m/z* calculated for $C_{13}H_{17}S$ $[M + H - HO_2C\text{-}CHClPh]^+$ 205.1046, found 205.1036.

Compound (±)-**30 [(±)-(*trans*-2-(*p*-tolyloxy)cyclohexyl 2-chloro-2-phenylethanoate].** Mixture of diastereomers (ratio of diastereomers determined using signal for H-2 at 4.18/4.08 ppm). Isolated via column chromatography (Rf 0.32, 95:5 hexane:ethyl acetate). Clear yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.41 (m, 2H, Ph), 7.27 (m, 3H, Ph), 7.07/6.99 (m, 8.4 Hz, 2H, Tol), 6.80/6.65 (dt, 8.4 Hz, 2.4 Hz, 2H, Tol), 5.30/5.23 (s, 1H, C**H**ClPh), 5.02 (m, 1H, H-1),

 ©ARKAT-USA, Inc.

4.18/4.08 (ddd, 9.6 Hz, 8.4 Hz, 4.2 Hz, 1H, H-2), 2.30/2.27 (s, 3H, tolyl-CH_3), 2.10 (m, 1H), 1.99 (m, 1H), 1.73 (m, 1H), 1.64 (m, 1H), 1.55-1.24 (m, 4H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 167.78 (C=O), 155.87 (C_q-O-C, Tol), 136.09/135.85 (C_q, Ar), 130.62/130.46 (C_q, Ar), 130.01/129.88 (2C, Tol-CH), 129.19/129.13 (1C, Ph-CH), 128.87/128.78 (2C, Ph-CH), 127.98 (2C, Ph-CH), 116.37/116.30 (2C, Tol-CH), 76.48 (C-2), 76.15 (C-1), 59.48/59.42 (**C**HClPh), 31.69, 29.64/29.48, 29.18, 22.99, 22.89, 22.77, 20.63 (tolyl-CH_3). HRMS: *m/z* calculated for $C_{21}H_{24}ClO_3$ $[M + H]^+$ 359.1409, found 359.1419; *m/z* calculated for $C_{13}H_{17}O$ $[M + H - HO_2C\text{-}CH(CH_3)Cl]^+$ 189.1274, found 189.1246.

Compound (±)-31 [(±)-(*trans*-2-(2,6-dimethylphenyloxy)cyclohexyl 2-chloro-2-phenyl-ethanoate]. Mixture of diastereomers (ratio of diastereomers determined using signal for H-1 at 5.11/5.05 ppm). Isolated via column chromatography (R_f 0.54, 9:1 hexane:ethyl acetate). Pale yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.5-7.3 (m, 5H, Ph-CH), 7.0-6.8 (m, 3H, $Ph(CH_3)_2$-CH), 5.30/5.13 (s, C**H**(Ph)Cl), 5.11/5.05 (ddd, 4.8 Hz, 8.4 Hz, 10.2 Hz, H-1), 3.94 (m, H-2), 2.26/2.15 (s, 6H, CH_3), 2.13/2.02 (m, 1H), 1.94/1.81 (m, 1H), 1.70/1.61 (m, 2H), 1.55-1.10 (m, 4H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 167.75(C=O), 154.30 (Ar-C_q), 131.18/131.01 (2C, Ar-C_q), 129.25/129.17 (Ph), 129.05/128.95 (2C, $Ph(CH_3)_2$), 128.90/128.79 (2C, Ph), 128.22/127.93 (2C, Ph), 123.47/123.37 ($Ph(CH_3)_2$), 80.07/79.86 (C-2), 78.19/77.59 (C-1), 59.60/59.29, 30.37/30.01, 29.77/29.64, 23.47/23.41, 23.36/23.31, 17.34/17.28 (2C, CH_3). HRMS: *m/z* calculated for $C_{22}H_{26}ClO_3$ $[M + H]^+$ 373.1565, found 373.1553; *m/z* calculated for $C_{14}H_{19}O$ $[M + H - HO_2C\text{-}CH(CH_3)Cl]^+$ 203.1431, found 203.1440; *m/z* calculated for $C_{14}H_{16}ClO_2$ $[M + H - HOPh(CH_3)_2]^+$ 251.0834, found 251.0851; *m/z* calculated for $C_{22}H_{29}ClNO_3$ $[M + NH_4]^+$ 390.1836, found 390.1880.

Compound (±)-32 [(±)-(*trans*-2-(cyclohexyloxy)cyclohexyl 2-chloro-2-phenylethanoate]. Mixture of diastereomers (ratio of diastereomers determined using signal for H-2 at 4.78/4.74 ppm). Isolated via column chromatography (Rf 0.48, CH_2Cl_2). Clear colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.49 (m, 2H, Ph), 7.36 (m, 3H, Ph), 5.32/5.32 (s, C**H**PhCl), 4.78/4.74 (m, 1H, H-2), 3.33/3.29 (m, 1H), 3.25/3.16 (m, 1H), 2.1-1.0 (m, 18H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 167.78/167.73 (C=O), 136.20/136.13 (C_q, Ph), 129.27/129.18 (Ph), 128.91/128.82 (2C, Ph), 128.10/128.04 (2C, Ph), 78.15/77.84 (C-2), 76.92/76.87, 76.23/76.12, 59.59/59.55, 33.43/33.25, 32.68/32.39, 31.57/31.34, 29.92/29.47, 25.81/25.71, 24.38/24.32, 23.55/23.38, 23.43/23.23. HRMS: *m/z* calculated for $C_{20}H_{28}ClO_3$ $[M + H]^+$ 351.1722, found 351.1738.

Compound (±)-33 [(±)-(*trans*-2-(*p*-tolylsulfonyl)cyclohexyl 2-chloro-2-phenylethanoate]. Mixture of diastereomers (ratio of diastereomers determined using signal for H-1 at 5.05/4.94 ppm). Isolated via column chromatography (F12-13: R_f 0.27, F15-16: R_f 0.31, 8:2 hexane:ethyl acetate). Clear colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.8-7.2 (m, 9 H, Ar), 5.09/4.62 (s, C**H**ClPh), 5.05/4.94 (dt, 4.5 Hz, 9.9 Hz, H-1), 3.29/3.18 (ddd, 4.8 Hz, 9.0 Hz, 10.8 Hz, H-2), 2.49/2.42 (s, 3H, tolyl-CH_3), 2.31/2.13 (m, 2H), 1.92-1.64 (m, 2H), 1.64-0.8 (m, 4H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 167.29/166.83 (C=O), 144.87/144.83 ($C_{q,Ar}$-S), 136.50/135.34 (C_q), 135.78/135.23 (C_q), 130.00/129.88, 129.43/129.31, 128.95/128.80, 128.72/128.40, 127.75, 72.44/72.33 (C-1), 65.44/64.90 (C-2), 59.20/58.36 (**C**H(CH_3)Cl), 30.64/30.53, 25.12/24.36,

 ©ARKAT-USA, Inc.

23.93/23.74, 23.05/22.91, 21.77/21.75. HRMS: *m/z* calculated for $C_{21}H_{24}ClO_4S$ $[M + H]^+$ 407.1079, found 407.1084; *m/z* calculated for $C_{21}H_{27}ClNO_4S$ $[M + NH_4]^+$ 424.1344, found 424.1308; *m/z* calculated for $C_{13}H_{17}O_2S$ $[M + H - HO_2CCHCl(C_6H_5)]^+$ 237.0944, found 237.0943; *m/z* calculated for $C_{42}H_{47}Cl_2O_8S_2$ $[M + H - HO_2CCHCl(C_6H_5)]^+$ 813.2084, found 813.1933.

Compound (±)-34 [(±)-*trans*-2-(methyl)cyclohexyl 2-chloro-2-phenylethanoate]. Mixture of diastereomers (ratio of diastereomers determined using signal for C**H**(Ph)Cl at 5.34/5.33 ppm). Isolated via column chromatography (Rf 0.54, 95:5 hexane:ethyl acetate). Clear yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.19 (m, 2H, Ph), 7.35 (m, 3H, Ph), 5.34/5.33 (s, C**H**(Ph)Cl), 4.46/4.43 (dt, 4.2 Hz, 10.2 Hz, H-1), 1.98/1.85 (m, 1H), 1.73 (m, 1H), 1.68 (m, 1H), 1.62-1.45 (m, 2H), 1.35-1.11 (m, 3H), 1.03 (m, 1H), 0.86/0.63 (d, 6.6 Hz, 3H, CH_3). ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 168.15 (C_q, C=O), 136.27/136.06 (C_q, Ph), 129.25/129.22 (Ph), 128.85/128.82 (2C, Ph), 127.99/127.97 (2C, Ph), 81.02/80.92 (C-1), 59.76/59.45 (**C**H(Ph)Cl), 37.25/37.11, 33.43, 31.50/31.12, 25.22/25.16, 24.67/24.56, 18.37/18.03 (CH_3). HRMS: *m/z* calculated for $C_{15}H_{20}ClO_2$ $[M + H]^+$ 267.1147, found 267.1139; *m/z* calculated for C_7H_{13} $[M + H - HO_2C$-$CH(Ph)Cl]^+$ 97.1012, found 97.1017; *m/z* calculated for $C_{15}H_{23}ClNO_2$ $[M + NH_4]^+$ 284.1417, found 284.1370.

Molecular modeling. Computations were performed using the CambridgeSoft ChemBioDraw 3D Ultra 12.0 program suite. The initial structures were constructed from the ester product with permanent configurations at C-2 of the acyl group as well as C-1 and C-2 of the cyclohexane ring. Subsequently, with the assumption that the transition state resembles the product to some extent (Eyring-Evans-Polanyi theory), a chlorine (or pyridinium) was introduced at the ester carbonyl, whose bond order was reduced from 2 to 1 and the formal oxidation state of oxygen was changed to -1. Variation of the transient configuration of the transition state carbon as well as of the permanent configuration on the acyl group resulted in all diastereomeric permutations. The corresponding enantiomeric structures were not considered computationally. The structures were then subjected to exhaustive dihedral angle searches for both substituents and were minimized into the global minima in the MM2 force field. Both R- and S-configurations of the transient sp3-carbon were considered. From this, the geometry was optimized without restrictions towards the transition state by the semi-empirical AM1 method initially, followed by subsequent geometry optimization at the B3LYP/3-21G and B3LYP/6-311G levels of theory. For the transition states including pyridine catalyst, the same method was used except that the formal charge at the pyridinium nitrogen was +1 and the formal charge at the oxygen was -1. Extended Hückel calculations generated the molecular orbitals for each structure. The xyz-coordinates of the lowest computed transition states for all pertinent diastereomeric permutations and the 2D representations of their LUMO are supplied in the Supplemental Material.

 ©ARKAT-USA, Inc.

Acknowledgements

The authors thank the National Science Foundation and a Major Research Instrumentation grant (CHE-0722654) for the funding of the JEOL ECA-600 NMR spectrometer. We also thank the Department of Chemistry at the University of the Pacific for financial support. We are thankful to Drs. Vyacheslav V. Samoshin and Mamoun M. Alhamadsheh for helpful suggestions and discussion.

References

1. Storch, G.; Trapp, O. *Angew. Chem. Int. Ed.* **2015**, *54*, 3580-3586. http://dx.doi.org/10.1002/anie.201412098
2. Ivšić, T.; Novak, J.; Došlić, N.; Hameršak, Z. *Tetrahedron* **2012**, *68*, 8311-8317. http://dx.doi.org/10.1016/j.tet.2012.07.035
3. Guan, Y.; López-Alberca, M. P.; Lu, Z.; Zhang, Y.; Desai, A. A.; Patwardhan, A. P.; Dai, Y.; Vetticatt, M. J.; Wulff, W. D. *Chem. Eur. J.* **2014**, *20*, 13894-13900. http://dx.doi.org/10.1002/chem.201404587
4. Kalck, P.; Urrutigoity, M. *Coord. Chem. Rev.* **2004**, *248*, 2193-2200. http://dx.doi.org/10.1016/j.ccr.2004.05.001
5. Arseniyadis, S.; Valleix, A.; Wagner, A.; Mioskowski, C. *Angew. Chem. Int. Ed. Engl.* **2004**, *43*, 3314-3317. http://dx.doi.org/10.1002/anie.200453956
6. Toueg, J. P., Prunet, J. *Org. Lett.* **2008**, *10*, 45-48. http://dx.doi.org/10.1021/ol702566c
7. Garzan, A.; Jaganathan, A.; Salehi Marzijarani, N.; Yousefi, R.; Whitehead, D. C.; Jackson, J. E.; Borhan, B. *Chem. Eur. J.* **2013**, *19*, 9015-9021. http://dx.doi.org/10.1002/chem.201300189
8. Sanji, T. T., M. *Organometallics* **2006**, *25*, 6159-6161. http://dx.doi.org/10.1021/Om060671r
9. Ordóñez, M.; Hernández-Fernández, E.; Rojas-Cabrera, H.; Labastida-Galván, V. *Tetrahedron: Asymmetry* **2008**, *19*, 2767-2770. http://dx.doi.org/10.1016/j.tetasy.2008.11.028
10. Martinez-Castaneda, A.; Rodriguez-Solla, H.; Concellon, C.; del Amo, V. *J. Org. Chem.* **2012**, *77*, 10375-10381. http://dx.doi.org/10.1021/jo3020352
11. Leclercq, L.; Suisse, I.; Agbossou-Niedercorn, F. *Eur. J. Org. Chem.* **2010**, *2010*, 2696-2700. http://dx.doi.org/10.1002/ejoc.200901075
12. Kawabata, T. N., M.; Takasu, K.; Fuji, K. *J. Am. Chem. Soc.* **1997**, *119*, 3169-3170. http://dx.doi.org/10.1021/Ja963275g

 ©ARKAT-USA, Inc.

13. Samoshin, A. V. V., J.; Curtis, M.; Samoshin, V.V.; Franz, A.H. *ARKIVOC* **2012**, *8*, 27-35. http://dx.doi.org/10.3998/ark.5550190.0013
14. Watson, A.; Hackbusch, S.; Samoshin, V.V.; Franz, A.H. *JUCR* **2014**, *13*, 38-42.
15. Lambert, J. B. B., B.M.; Kuang, K. *J. Org. Chem.* **1999**, *64*, 9241-9245. http://dx.doi.org/10.1021/Jo991536
16. Al Hazmi, A. M.; Sheikh, N. S.; Bataille, C. J. R.; Al-Hadedi, A. A. M.; Watkin, S. V.; Luker, T. J.; Camp, N. P.; Brown, R. C. D. *Org. Lett.* **2014**, *16*, 5104-5107. http://dx.doi.org/10.1021/ol502454r

 ©ARKAT-USA, Inc.